

U.S.S.N. 09/445,439

Filed: February 23, 2000

**AMENDMENT AND RESPONSE TO OFFICE ACTION****In the Claims**

Claim 1-100 (canceled)

101. (canceled) A method of administering one or more physiologically effective substances to the central nervous system comprising

a) administering to a patient in need thereof nanoparticles consisting essentially of a polymeric material comprising one or more monomeric or oligomeric precursors polymerized in the presence of one or more stabilizers, and loaded with one or more physiologically effective substances, wherein the stabilizers are selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxyated ethers, alkoxyated esters, alkoxyated mono-, di-, and triglycerides, alkoxyated phenols and diphenols, sodium stearate, metal salts of carboxylic acids, metal salts of alcohol sulfates, metal salts of sulfosuccinates, and compounds of the formula



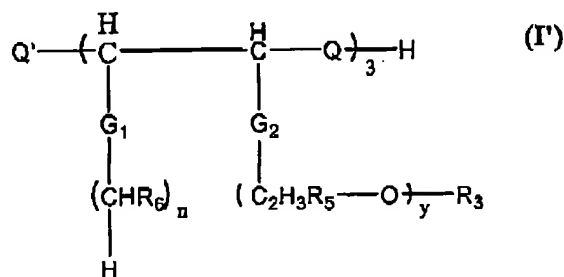
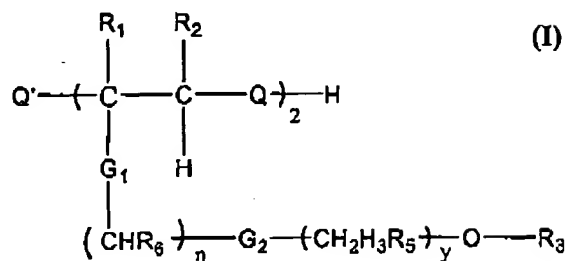
wherein y is in the range of 4 to 18 and x is in the range of 1 to 18,

compounds of the formula (I) or (I')

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wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_5$ , and  $\text{R}_6$  are identical or different and represent hydrogen and a methyl or ethyl group,

wherein  $\text{Q}$  represents a valency, oxygen or an ester or amide bridge and  $\text{Q}'$  denotes hydrogen if  $\text{Q}$  represents a valency or oxygen, and is a hydroxyl or amino group if  $\text{Q}$  represents an ester or amide bridge,

wherein  $X$  is an integer from 3 to 50, if  $\text{Q}$  is a valency or oxygen, and an integer from 3 to 1000 if  $\text{Q}$  is an ester or amide function, and

wherein  $\text{G}_1$  and  $\text{G}_2$  are a valency oxygen or an ester or amide group, it being possible for the two groups to be identical or different,  $n$  is an integer from 4 to 44,  $y$  is an integer from 2 to 50, and  $\text{R}_3$  is hydrogen or a lower alkyl having 1-6 C atoms, and mixtures of two or more said substances, and; by polymerizing one or more monomers or

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oligomeric precursors of said polymer material or both, in the presence of said one or more physiologically effective substances and in the presence of said stabilizers.

102. (currently amended) A method for preparing a nanoparticle formulation for administering one or more physiologically effective substances to the central nervous system comprising:

a) providing nanoparticles consisting essentially of a polymeric material comprising one or more monomeric or oligomeric precursors polymerized in the presence of one or more stabilizers, and loaded with one or more physiologically effective substances wherein the one or more stabilizers are selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, ~~polyoxamer-188~~, polyoxamines, alkoxyated ethers, alkoxyated esters, alkoxyated mono-, di-, and triglycerides, alkoxyated phenols and diphenols, sodium stearate, metal salts of carboxylic acids, metal salts of alcohol sulfates, metal salts of sulfosuccinates, and compounds of the formula

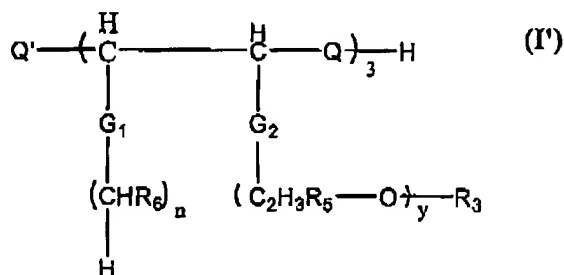
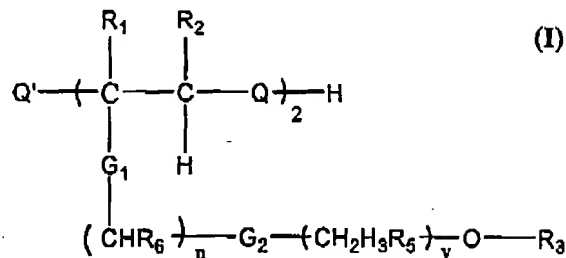


wherein y is in the range of 4 to 18 and x is in the range of 1 to 18, compounds of the formula (I) or (I')

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wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_5$ , and  $\text{R}_6$  are identical or different and represent hydrogen and a methyl or ethyl group,

wherein  $\text{Q}$  represents a valency, oxygen or an ester or amide bridge and  $\text{Q}'$  denotes hydrogen if  $\text{Q}$  represents a valency or oxygen, and is a hydroxyl or amino group if  $\text{Q}$  represents an ester or amide bridge,

wherein  $X$  is an integer from 3 to 50, if  $\text{Q}$  is a valency or oxygen, and an integer from 3 to 1000 if  $\text{Q}$  is an ester or amide function,

wherein  $\text{G}_1$  and  $\text{G}_2$  are a valency oxygen or an ester or amide group, it being possible for the two groups to be identical or different,  $n$  is an integer from 4 to 44,  $y$  is an integer from 2 to 50, and  $\text{R}_3$  is hydrogen or a lower alkyl having 1-6 C atoms, and mixtures of two or more said substances, and; by polymerizing one or more monomers or

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oligomeric precursors of said polymer material or both, in the presence of said one or more physiologically effective substances and in the presence of said stabilizers; and optionally

b) loading an effective amount of one or more physiologically effective substances to be delivered to the central nervous system of the patient into or onto the nanoparticles or both; and optionally

c) providing the nanoparticles in a medium allowing the transport of the nanoparticles to the central nervous system of a patient.

103. (canceled) The method of claim 101, wherein the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation and crosslinking oligomers or polymers or both, in solution.

104. (canceled) The method according to claim 101, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.

105. (previously presented) The method of claim 102, wherein the loading step comprises mixing the nanoparticles with a solution of one or more physiologically

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effective substances and allowing a sufficient time for an effective amount of the physiologically effective substances to be adsorbed onto or absorbed by the nanoparticles or both.

106. (canceled) The method of claim 101 wherein the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation and crosslinking oligomers or polymers or both, in solution.

107. (canceled) The method according to claim 101, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.

108. (previously presented) The method of claim 102, wherein the loading step comprises mixing the nanoparticles with a solution of one or more physiologically effective substances and allowing a sufficient time for an effective amount of the physiologically effective substances to be adsorbed onto or absorbed by the nanoparticles or both.

109. (canceled) The method of claim 101, wherein the stabilizers are selected from the group consisting of polysorbate 85 and dextran 12,000 and mixtures thereof.

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110. (previously presented) The method of claim 102, wherein the stabilizers are selected from the group consisting of polysorbate 85 and dextran 12,000 and mixtures thereof.

111. (canceled) The method of claim 101, wherein the physiologically effective substances are selected from the group consisting of a therapeutic substance and a diagnostic substance.

112. (previously presented) The method of claim 102, wherein the physiologically effective substances are selected from the group consisting of a therapeutic substance and a diagnostic substance.

113. (canceled) The method of claim 101, wherein the physiologically effective substances have central nervous system activity but cannot cross the blood brain barrier without modification or without a carrier.

114. (previously presented) The method of claim 102, wherein the physiologically effective substances have central nervous system activity but cannot cross the blood brain barrier without modification or without a carrier.

115. (canceled) The method of claim 101, wherein the physiologically effective substances are selected from the group consisting of drugs acting at synaptic sites and neuroeffector junctional sites, general and local analgesics; hypnotics and sedatives, drugs for the treatment of psychiatric disorder; anti-epileptics and anti-convulsants; drugs for the treatment of Parkinson's and Huntington's disease, aging and Alzheimer's

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disease, excitatory amino acid antagonists, neurotropic factors and neuroregenerative agents; tropic factors, drugs aimed at the treatment of CNS trauma or stroke; drugs for the treatment of addiction and drug abuse; antacoids and anti-inflammatory drugs; chemotherapeutic agents for parasitic infections and diseases caused by microbes; immunosuppressive agents and anticancer drugs; hormones and hormone antagonists; heavy metals and heavy metal antagonists; antagonists for non-metallic toxic agents, cytostatic agents for the treatment of cancer; diagnostic substances for use in nuclear medicine; immunoactive and immunoreactive agents; transporter inhibitors; antibiotics; antispasmodics; antihistamines; antinauseants; relaxants; stimulants; sense and antisense oligonucleotides; cerebral dilators; psychotropics; antimaniacs; vascular dilators and constrictors; atihypertensives; drugs for migraine treatment; hypnotics; hyperglycemic and hypoglycemic agents; minerals and nutritional agents; anti-obesity drugs; anti-asthmatics; and mixtures thereof.

116. (canceled) The method of claim 115, wherein the psychiatric disorders comprise depression and schizophrenia.

117. (previously presented) The method of claim 102, wherein the physiologically effective substances are selected from the group consisting of drugs acting at synaptic sites and neuroeffector junctional sites, general and local analgesics; hypnotics and sedatives, drugs for the treatment of psychiatric disorder; anti-epileptics and anti-convulsants; drugs for the treatment of Parkinson's and Huntington's disease,



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aging and Alzheimer's disease, excitatory amino acid antagonists, neurotropic factors and neuroregenerative agents; tropic factors, drugs aimed at the treatment of CNS trauma or stroke; drugs for the treatment of addiction and drug abuse; antacoids and anti-inflammatory drugs; chemotherapeutic agents for parasitic infections and diseases caused by microbes; immunosuppressive agents and anticancer drugs; hormones and hormone antagonists; heavy metals and heavy metal antagonists; antagonists for non-metallic toxic agents, cytostatic agents for the treatment of cancer; diagnostic substances for use in nuclear medicine; immunoactive and immunoreactive agents; transporter inhibitors; antibiotics; antispasmodics; antihistamines; antinauseants; relaxants; stimulants; sense and antisense oligonucleotides; cerebral dilators; psychotropics; antimaniacs; vascular dilators and constrictors; atihypertensives; drugs for migraine treatment; hypnotics; hyperglycemic and hypoglycemic agents; minerals and nutritional agents; anti-obesity drugs; anti-asthmatics; and mixtures thereof.

118. (previously presented) The method of claim 117, wherein the psychiatric disorders comprise depression and schizophrenia.

119. (canceled) The method of claim 101, wherein the diagnostic substance is selected from the group consisting of substances for nuclear medicine and radiation therapy.

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120. (previously presented) The method of claim 102, wherein the diagnostic substance is selected from the group consisting of substances for nuclear medicine and substances for radiation therapy.

121. (canceled) The method of claim 101, wherein the medium allows the transport of the nanoparticles to the target within the patient after administration is selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts or buffers or a mixture thereof, and any other solution acceptable for administration to the patient.

122. (previously presented) The method of claim 102, wherein the medium allows the transport of the nanoparticles to the target within the mammal after administration is selected from the group consisting of water, physiologically-acceptable aqueous solutions containing salts or buffers or a mixture thereof, and any other solution acceptable for administration to the patient.

123-131. (canceled)

132. (canceled) The method of claim 101, wherein the nanoparticles are made of polybutylcyanoacrylate.

133. (previously presented) The method of claim 102, wherein the nanoparticles are made of polybutylcyanoacrylate.

134. (canceled)

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135. (previously presented) The method of claim 102, wherein the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation, and crosslinking oligomers or polymers or both, in solution.

136. (previously presented) The method according to claim 102, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.